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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,765	11/21/2003	Rima Kaddurah-Daouk	AVZ-001CPUSCN2RCE	1461

959 7590 11/18/2008

LAHIVE & COCKFIELD, LLP
FLOOR 30, SUITE 3000
ONE POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1639	
MAIL DATE	**DELIVERY MODE**
11/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,765	KADDURAH-DAOUK ET AL.	
	Examiner	Art Unit	
	JEFFREY S. LUNDGREN	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Following the Office Action mailed on September 20, 2007, Applicants amended the claims in their reply of March 19, 2008, to which was issued a Restriction Requirement mailed July 29, 2008. In response Applicants have elected the species "reducing symptoms in patients having Huntington's disease". However, upon further consideration, the species requirement is withdrawn.

Accordingly, claims 22-39 are pending in the instant application, and are the subject of the Office Action below.

Previous Rejections Withdrawn

The previous rejections made in the Office Action mailed on September 20, 2007, have been overcome in view of Applicants' amendment to claim 22 deleting the phrase "or a creatine analog", and are not applicable to newly introduced claims 30-39.

Claim Rejections - 35 USC § 112 – Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". See *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Some of these factors may include:

(1) the breadth of the claims;
(2) the nature of the invention;

(3) the state of the prior art;
(4) the level of one of ordinary skill;
(5) the level of predictability in the art;
(6) the amount of direction provided by the inventor;
(7) the existence of working examples; and
(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims and nature of the invention:

The claimed invention is directed towards both methods of treating Huntington's disease and slowing the progression of the disease. For example, claim 22 reads:

> A method for treating a subject with Huntington's disease, comprising administering to the subject an effective amount of creatine, creatine phosphate or a salt thereof sufficient to reduce or ameliorate Huntington's disease, and further comprising coadministering to the subject a neurotransmitter, a neurotransmitter analog, an immunomodulating agent, or an immune suppressive agent.

Amended claim 22 in the Reply dated March 19, 2008.

Claim 30 is similar and has overlapping scope, and reads:

> A method for reducing progression of Huntington's disease in a subject, comprising administering to the subject an effective amount of creatine or a salt thereof sufficient to reduce progression of Huntington's disease in said subject.

New claim 30 in the Reply dated March 19, 2008

The nature of the invention is directed towards the administration of the compound creatine, creatine phosphate or a salt thereof to a patient diagnosed with Huntington's disease or at risk for Huntington's disease (*i.e.*, preventing):

> "The present invention pertains to methods of treating diseases of the nervous systems ***in an individual afflicted with such a disease*** by administering to the afflicted individual an amount of a compound or compounds which modulate one or more of the structural or functional components of the creatine kinase/phosphocreatine system sufficient to ***prevent, reduce or ameliorate the symptoms of the disease***. Compounds which are effective for this purpose include creatine, creatine phosphate, and analogs of creatine or creatine phosphate."

Specification, page 4, first paragraph (emphasis added).

The claimed treatment and symptomatic amelioration methods are stated to include the following:

> "The language "treating diseases of the nervous system" is intended to include ***prevention of the disease, amelioration and/or arrest of a preexisting disease, and the elimination of a preexisting disease***. The creatine analogs described herein have both curative and prophylactic effects on disease development and progression."

Specification, page 8, second paragraph.

The nature of Huntington's disease is described as follows:

> HD is an autosomal dominant disorder of midlife onset, characterized clinically by movement disorder, personality changes, and dementia often leading to death in 15-20 years. The neuropathologic changes in the brain are centered in the basal ganglia. Loss of a class of projection neurons, called "spiny cells" because of their prominent dendritic spinous processes, is typical. This class of cells contains gamma-aminobutyric acid (GABA), substance P, and opioid peptides. Linkage studies have localized the gene for HD to the most distal band of the short arm of chromosome 4. ***No treatments are available that have been shown to retard progression of the disease***.

Specification, paragraph bridging pages 14 and 15 (emphasis added).

The amount of direction provided by the inventor and the existence of working examples:

As noted above, Applicants assert that their invention is directed to the treatment and prevention of Huntington's disease by the administration of creatine, creatine phosphate or a salt thereof. Part of Applicants' theory behind their claimed treatment methods is that since Huntington's disease appears to correlate with reduced energy metabolism, that one treatment option is to increase metabolic energy in brain/neuronal cells (page 15, lines 2-4; page 17, line 21 through page 18, line 6; page 21, lines 8-25; and all of page 34).

Applicants provide certain examples in their disclosure, including an example to determine whether or not creatine is neuroprotective to disorders that purportedly progress by reductions in metabolic brain energy. In Example 1, Applicants provide control and test rats; the test rats receive a "prophylactic" dose of creatine, followed by administration of malonate,

whereas the test rats only receive a dose of malonate. Applicants are of the opinion that administration of the chemical compound malonate produces striatal lesions in the brain similar to those that are observed in patients suffering from Huntington's disease. Therefore, according to Applicants, a reduction in striatal lesions in the test subjects compared to the control upon the administration of malonate would serve to demonstrate that creatine "reduces the progression" of Huntington's disease. Figure 1 shows the results in the malonate rat model.

Applicants also provide a declaration under 37 C.F.R. § 1.132 from Dr. Belinda Nivaggioli (hereinafter "Nivaggioli"), wherein it is asserted that creatine "treats" Huntington's disease (page 1, second paragraph). Nivaggioli states that a study has been conducted wherein thirteen genetically confirmed patients with Huntington's disease (three clinically unaffected and ten clinically affected) were each given 10 g of creatine daily for a period of 24 months. For the control population, Nivaggioli states that "four age-matched spouse controls" were recruited for the study (page 2, paragraph 4). Applicants conclude that based on TMS, functional capacity and neuropsychology testing, no significant differences were observed at 12 months or 24 months (page 3, paragraphs 2-5).

Nivaggioli also suggests that there is evidence that the administration of creatine prevents Huntington's disease as determined by morphometric imaging:

> "Morphometric neuroimaging was performed in all subjects… Creatine reduced the rate of thinning in almost every region, and the rate of change was determined for each region for the group while on creatine. Creatine reduced the rate of thinning in almost every region, and the rate of change was statistically significant for several regions and amounted to about a 30% slowing.

Nivaggioli Declaration, page 5, second paragraph.

The level of skill in the art:

Those of skill in the art of developing treatments for Huntington's disease are likely to have at least a graduate level degree in the biomedical arts and relevant experience with clinical and/or laboratory practice investigating Huntington's disease. Additionally, these persons will have significant experience with assessing the stage of Huntington's disease, the use of animal models for comparing treatment data, and be familiar with the broad range of complex factors

that need to considered for understanding both the etiology of Huntington's and its symptomatic assessments.

The state of the art and the level of predictability in the art:

Contrary to the general disclosure in Applicants specification, Applicants' Example 1 describing the laboratory study involving prophylactic creatine administration to rats prior to malonate dosing, and the experimental monitoring of Huntington's patients as detailed in items 5 and 6 of the Nivaggioli Declaration that includes morphometric imaging, the art suggest that creatine does not treat or reduce the progression of Huntington's disease. The art also shows that the models that Applicants rely upon are premature and not conclusive for determining that creatine can reduce the progression of Huntington's.

Starting with Applicants' Example 1 using the rat model with malonate, the art suggests that such models are not yet suitable for determining the prophylactic effects of suspected Huntington's disease treatments. For example, consider Lee[1] who teaches that such a model is not necessarily appropriate for assessing Huntington's disease although certain effects of malonate are similar to Huntington's striatal lesions:

> "Mitochondrial toxins like 3-nitropropionic acid (3-NP) and malonate, functioning as the inhibitors of the complex II of mitochondrial respiratory chain, have been found to effectively induce specific behavioral changes and selective striatal lesions in rats and non-human primates mimicking those in HD."

Lee, Abstract; and:

> "However, the pathogenic mechanisms of selective striatal lesions in 3-NP neurotoxicity are not well known. As an inhibitor of succinate dehydrogenase (SDH), 3-NP can affect the energy metabolism of neurons in different areas of the brain. As shown in the past, the extent of SDH inhibition following 3-NP treatment may be related to the selectivity of the brain lesions. Vulnerable rats developed a region within striatum where SDH activity was fully depleted (Alexi et al., 1998). In addition, the release of dopamine, which was increased in striatum following 3-NP application, may also play a role (Nishino et al., 1997; Fernagut et al., 2002a; Maragos et al., 1998, 2002). Systemic low-dose 3-NP only induced a significant reduction of the striatal volume in dopamine transporter

[1] Lee *et al.*, *Progress in Neurobiology*, *72*:87-110 **(2004)**.

> knockout mice, independent of the degree of SDH inhibition, also suggesting the role of dopamine modulation in excitotoxicity within the nigrostriatal system (Fernagut et al., 2002b). Recently, adenosine A2a receptors, which were rich and colocalized with dopamine D2 receptors in striatum, were shown to be involved in 3-NP-induced striatal lesions (Ribeiro et al., 2003; Blum et al., 2003). Reduction of A2a receptor expression in striatum had been found to be one of the earliest characteristic changes in both HD patients and transgenic mice of HD (Blum et al., 2003), consistent with the selectivity of striatal lesion in 3-NP intoxication."

Lee, page 89, col. 1, first paragraph.

Lee also addresses a number of other factors that contribute to the rat model not being representative, such as rat-primate differences (page 89, col. 2, second paragraph), and age-related variables (page 89, col. 2, first paragraph).

Regarding Applicants' characterization of their morphometric neuroimaging results, the Nivaggioli Declaration does not provide sufficient detail of the particular method used, how their particular model and data analysis system is accepted-methodology by those assessing Huntington's disease, nor state to the extent that Dr. Nivaggioli has experience in this complex field of radiology. The curriculum vitae provided with the Declaration does not identify Dr. Nivaggioli as having experience in the field of radiology or morphometric imaging.

Instead, the art suggests that morphometric neuroimaging does not have an established protocol for assessing Huntington's disease even though certain observational features can be obtained. In a reference dealing with morphometric neuroimaging as it relates to Huntington's disease, Kipps[2] states that none of results show and reduced symptoms of HD:

> "***Progression of disease could not be documented on clinical assessment in this study. This was despite significant, albeit minor, differences in selected motor and cognitive subscores at both initial and follow up assessments***. The residual variance in clinical scores not attributable to HD gene status is large, and inevitably larger when different clinicians are responsible for the early and late assessments.
>
> Although it is perhaps not surprising that clinical instruments effective in established HD are ***insensitive to pathologic progression in preclinical HD***, it is indeed remarkable that statistical imaging characterises the

[2] Kipps *et al.*, *J. Neurol. Neurosurg. Psychiatry*, *76*:650-655 **(2005)**.

> distribution and extent of progression in this group with such clarity. We have shown progression of basal ganglia atrophy in HD with an objective, reproducible technique, over a time interval suitable for a trial of intervention, in a mutation-positive preclinical population most likely to receive benefit."

Kipps, page 655, col. 1, second paragraph (emphasis added).

Furthermore, there is sufficient evidence to show that observed creatine effects on the brain correlate with other disorders, such as boderline personality disorders, and raise a substantial doubt that the results summarized in the Nivaggioli Declaration are not limited to reducing the progression of Huntington's disease. For example, see the reference by van Elst[3]:

> "In order to detect possible links between structural and neurochemical brain abnormalities we applied high resolution morphometric imaging and short-echo time absolute-quantification magnetic resonance spectroscopy (MRS) at the left hand side to the amygdala in 12 patients with borderline personality disorder (BPD) and 10 group-matched healthy controls. Confirming earlier reports we found a significant 11–17% reduction of amygdalar volumes in patients with BPD. In addition there was a significant 17% increase of left amygdalar creatine concentrations in BPD patients. Left amygdalar creatine concentration correlated positively with measures of anxiety and negatively with amygdalar volume. This pilot study of simultaneous amygdalar morphometry and spectroscopy in BPD reveals a possible link between amygdalar volume loss, psychopathology and neurochemical abnormalities in terms of creatine signals."

van Elst, Abstract.

And in the general conclusion of creatine from a clinical perspective, Ryu[4] shows that that creatine administration does not results in an effective means for reducing the progression of Huntington's disease:

> While there have been several clinical trials of creatine in HD, ***none have been powered to detect significant slowing of progression and none have revealed any improvement in clinical measures***.

Ryu, page 200, col. 2, second paragraph (emphasis added); and:

> "Bender and colleagues used MRS to examine another biomarker of creatine's activity in HD patients treated with ***20 g/day for 5 days,***

[3] van Elst *et al.*, *Neuroscience Letters*, *417*:36-41 (**2007**).
[4] Ryu *et al.*, *Pharmacology & Therapeutics*, *108*:193-207 (**2005**).

> ***followed by 6 g/day for 8 –10 weeks***. They demonstrated a significant reduction in glutamate levels in the parietooccipital cortex. This is very interesting because glutamate release and excitotoxicity are enhanced by energy deficiency and are considered to play a significant role in the pathogenesis of HD. ***None of these studies were sufficiently powered to be informative about whether or not creatine slows the clinical progression of HD***, however, they do attest to its safety and tolerability and favorable effects on serum and brain levels of creatine and on biomarkers of HD pathology. The optimal dose to use in a definitive efficacy study for HD is not yet certain. The most efficacious neuroprotective dose of creatine in transgenic mouse studies was 2% of the diet, corresponding to ***30–35 g/day in HD patients weighing 70 kg, suggesting that the dose of creatine supplementation in HD patients may have been underestimated***. While mouse and human bioavailability may not correspond well, such a dose is at least feasible for humans."

Ryu, page 200, col. 2, second paragraph through page 201, col. 1 (emphasis added).

The quantity of experimentation needed to make or use the invention:

Although Applicants disclosure, working examples and evidence provide by way of declaration suggest that there may be a relationship between creatine dosing and certain neurological effects, the art relating to Huntington's disease assessment and modeling would suggest that Applicants' disclosure and/or conclusions are not commensurate with the claimed invention. In view of the complexity of the clinical studies, the use of animal models, molecular biology and etiology of Huntington's disease, the skilled artisan would be left with and undue amount of experimentation in order to practice the invention as claimed.

Conclusions

No claim is allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Christopher Low, can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JSL/

/Christopher S. F. Low/
Supervisory Patent Examiner, Art Unit 1639
12 Nov 2008